REMARKS

Introductory Comments:

Claims 21-40 were examined in the Office Action under reply. Applicant thanks the Examiner for reconsidering the previous Restriction Requirement and rejoining claims 21 and 23 with claims 22 and 24-40.

The claims stand variously rejected under 35 U.S.C. § 112, first paragraph (claims 21-40); 35 U.S.C. §112, second paragraph (claims 21-40); 35 U.S.C. §102 (claims 22 and 24-40); and 35 U.S.C. §103 (claims 22 and 24-40). Additionally, claims 21-40 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting. These rejections are respectfully traversed as discussed more fully below.

Overview of the Above Amendments:

Claims 21-23 and 25-29 have been amended to recite the subject invention with greater particularity. Specifically, claims 21-23 have been amended to incorporate terminology present in previous claim 30 and now recite that the protein is an "unglycosylated, transmembrane protein" with a molecular weight of about 24 kd "as determined by SDS-PAGE." Additionally, the claims recite that the protein is "stable to acetone precipitation" and "specifically binds the E2 protein of hepatitis C virus." Claims 22 and 23 have also been amended to delete the term "functionally equivalent variant." Claim 25 has been amended for antecedent basis reasons and claim 26 has been amended to correct a spelling error. Additionally, claims 25-29 now ultimately depend from claim 22 and hence recite a "composition" in the preamble. These composition claims correspond to previous claims 35-40.

Support for the foregoing amendments may be found throughout the specification at, e.g., page 3, lines 12-13; page 4, line 1; page 5, lines 9-11; and page 6, lines 15-17.

Claims 24 and 30-40 have been canceled in order to hasten prosecution. Cancellation of these claims is without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicant expressly reserves the right to file one or more continuing applications hereof containing these canceled claims.

Rejection of Claims under 35 U.S.C. §112, First Paragraph:

(A) The Office rejected claims 21-23 under 35 U.S.C. §112, first paragraph, asserting that the specification "does not teach that administration of a protein having a molecular weight of about 24 kD, or a functionally equivalent variant or fragment thereof, and capable of binding to E2 of HCV, in fact is of any therapeutic value to a human subject." Office Action, page 3. Applicant disagrees with these contentions and respectfully submits that the claims are indeed fully enabled.

It is well settled that the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*Ex parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986). Specifically, in order to comply with the enablement requirement of 35 U.S.C. §112, first paragraph, the specification need only set forth such information as is sufficient to allow one of ordinary skill in the art to make and use the invention. How such a teaching is accomplished, either by the use of illustrative examples or by broad terminology, is of no importance since a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of §112 unless there is

reason to doubt the objective truth of the statements relied upon therein for enabling support (*In re Marzocchi*, 169 USPQ 367 (CCPA 1971)). The burden is on the Office to explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the applicant's claim: the reasoning must be supported by current literature as a whole and the Office must prove the disclosure requires undue experimentation. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971). The Office has failed to carry its burden.

More than adequate information has been provided in order to enable one of skill in the art to make and use the invention. An extensive discussion of methods of making and administering the 24 kD proteins and fragments thereof as claimed is found throughout the specification and examples. The described methods could readily be used to practice the invention without undue experimentation. The Office is reminded that even a large amount of experimentation is permitted under §112, first paragraph, provided it is routine. *Ex parte Jackson*, 217 USPQ 804, 807 (POBA 1982) (a claim is acceptable under §112 even if it requires extensive experimentation, as long as the experimentation is routine). In light of the disclosure in the application, and in view of the state of the art, applicant submits that the present claims are indeed enabled.

The specification teaches that the 24 kD protein is of therapeutic value. For example, HCV E2 was shown to bind to the purified 24 kD protein, as well as to cells expressing the 24 kD protein. Additionally, as explained in the examples, E2 binding was disrupted by E2 reduction, as well as by E2 deglycosylation, indicating that E2 as it occurs in its native conformation (i.e., as it would be found in the virus particle) would be expected to bind the 24 kD protein. Later reports confirm that CD81 binds to an HCV E1E2 heterodimer which is properly folded and interacts with conformation-dependent monoclonal antibodies. See, Lambot et al., *J. Biol. Chem.* (2002) 277:20625-20630, the abstract of which accompanies this response. Thus, the E2 binding protein has been shown to bind HCV using a

molecule that retains the native conformation as found *in vivo*. Applicant submits that this is more than adequate evidence that the 24 kD protein binds HCV. Although these data represent results from *in vitro* assays, such assays are traditionally used in the relevant field and are considered indicative of therapeutic efficacy. Thus, one of skill in the art would readily accept applicant's statements in the application regarding efficacy of the claimed invention. For example, page 6, lines 8-13 of the application state:

> Since the infection mechanism of HCV appears to depend, in part, upon the availability of a cell surface receptor, making available a soluble form of the protein of the invention will act as an antagonist of binding of HCV to the cellular receptor thus reducing or preventing the infection process and thereby treating the disease.

As explained above, these statements must be accepted by the Office unless there is acceptable reasoning and evidence to dispute them.

The Office points to statements in Pileri et al., *Science* (1998) 282:938-941 ("Pileri-1") regarding additional factors that may be required for HCV fusion or infectivity. However, Pileri et al., *Hepatology* (1999) 29:990-992 ("Pileri-2" which accompanies the Supplemental Information Disclosure Statement provided herewith) explains that multiple receptors or coreceptors are often required for internalization of viruses. See, e.g., page 990, column 2, second full paragraph of Pileri-2. In fact, Petracca et al., *J. Virol.* (2000) 74:4824-4830 ("Petracca" which accompanies the Supplemental Information Disclosure Statement), supports applicant's statements regarding therapeutic efficacy. As reported in Petracca, CD81 is a cellular receptor for HCV and binds to HCV E2 with high affinity, analogous to the HIV gp120-CD4 interaction. The authors propose that the protein serves as an HCV attachment receptor rather than as a receptor for virus entry and may serve to concentrate virus particles at the cell surface for subsequent interaction with an entry receptor. It is of no consequence that additional factors might be needed for infectivity or internalization. Binding, in and of itself, leaves less circulating virus and therefore serves to decrease viral load. Eliminating or reducing the amount of circulating virus using applicant's

protein, eliminates or reduces the amount of available virus for interacting with any cell surface receptor. Thus, less HCV is internalized and hence less virus replicates. Reducing viral load, whether or not the virus is completely eliminated, is useful in and of itself. For example, HCV viral load is known to be correlated with the development of heptocellular carcinoma. See, Ishikawa et al., *J. Gastroenterol. Hepatol.* (2001) 16:1274-1281, the abstract of which accompanies this response.

Moreover, only claim 21 relates to a method of treatment. Claims 22 and 23 are directed to compositions and methods of preparing a composition, respectively. The Office argues: "The intended use of the composition of claims 22 and 23 encompasses use as a pharmaceutical for treatment of human HCV infection." However, the claims do not impose the limitation of therapeutic administration *in vivo*. The specification does teach the use of the composition for therapeutic and/or prophylactic administration. However, "a positive limitation from the specification cannot be read into a claim that does not impose that limitation" (MPEP §2106). As explained *In re Prater*, 415 F.2d 1393, 1404-05 (CCPA 1969), "reading a claim in light of the specification, to thereby interpret limitations explicitly recited in the claim, is a quite different thing from "reading limitation of the specification into a claim," to thereby narrow the scope of the claim by implicitly adding disclosed limitations which have no express basis in the claim." The court found that it was impermissible to import subject matter from the specification into the claims. In the present case, in making the rejection, the Examiner is impermissibly importing a therapeutic use limitation from the specification into the composition of matter claims, where such a limitation is not recited. One possible use of the composition is not an element of claims 22 and 23.

In fact, the specification is clear that there are multiple uses for the proteins of the invention and compositions comprising the same. For example, page 7, line 19 through page 8, line 21 explains that the proteins are useful in

diagnostic assays for HCV infection, e.g., in ELISAs or RIAs and other competitive assays.

For all of the foregoing reasons, then, applicant submits that when the relevant enablement factors are actually weighed, as they must be, the balance tips heavily in favor of enablement. The Office's assertion that there is some level of unpredictability in the art does not outweigh the enablement provided by the working examples and detailed guidance supplied by applicant's specification, the state of the art, the relative skill of those in the art, and the quantity of experimentation necessary to practice the invention throughout the scope of the claims. Reconsideration and withdrawal of the rejection of claims 21-23 for lack of enablement is thus respectfully requested.

(B) The Office rejected claims 21-40 under 35 U.S.C. §112, first paragraph, asserting that the specification does not provide written description for the claimed invention. The Examiner correctly notes that the specification describes the 24 kD protein, but argues that functionally equivalent variants and fragments are not adequately described. In support of this statement, the Office quotes *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1898, 1406 (Fed. Cir. 1997): "An adequate written description of a DNA...requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Office Action, page 5. However, the present claims pertain to protein compositions not DNA. Moreover, the recitations present in canceled claim 30, regarding the physical characteristics of the 24 kD protein, have been incorporated into all independent claims. Thus, the recited protein is indeed precisely defined based on measurable characteristics, and thus fragments of this protein are indeed described.

It is axiomatic that compliance with the written description requirement of 35 USC §112, first paragraph only requires that the application contain sufficient disclosure, either expressly or inherently, to make clear to persons skilled in the art that the applicant was in possession of the subject matter claimed. See, e.g., *In re Mott*, 190 USPQ 536, 541 (CCPA 1976); and *Ex parte Harvey*, 3 USPQ2d 1626, 1627 (BOPAI 1987). The specification also preferably excludes what is commonly known. One of skill in the art would readily understand that applicant was in possession of the claimed protein and fragments thereof. Applicant describes and claims the 24 kD protein and fragments of the protein throughout the specification by physical characteristics, namely, the protein is an unglycosylated, transmembrane protein having a molecular weight of about 24 kd as determined by SDS-PAGE; the protein is stable to acetone precipitation; and the protein or fragment thereof specifically binds to the E2 protein of HCV. Accordingly, the claims are believed to comply with the written description requirement of 35 U.S.C. §112, first paragraph. The Examiner is respectfully requested to withdraw the rejection.

(C) The Examiner rejected claims 21-29 and 35 under 35 U.S.C. §112, first paragraph, asserting that the specification does not "reasonably provide enablement for any and all functionally equivalent variants or fragments" of the 24 kD protein. Applicant traverses the rejection. The amended claims include the recitations of claim 30 which was not subject to the rejection. Additionally, the term "functionally equivalent variants" has been eliminated from the claims. Moreover, applicant submits that fragments of the recited protein are indeed enabled. Once the 24 kD protein is obtained using the methods described in the specification, it is routine to obtain fragments thereof, e.g., by enzymatically or chemically cleaving the protein. Fragments so obtained can be readily tested for binding to HCV E2 using the methods described in the specification. Thus, contrary to the Office's assertions, one of skill in the art could obtain functional fragments of the 24 kD protein, without undue experimentation. Withdrawal of

the rejection under 35 U.S.C. §112, first paragraph is therefore respectfully requested.

Rejection of Claims 21-40 under 35 U.S.C. §112, Second Paragraph:

The Office rejected claims 21-40 under 35 U.S.C. §112, second paragraph, asserting that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

(A) The Office asserted that the use of the terminology "functionally equivalent" in claims 21-24 is indefinite because "it is not clear what equivalent function is required in order to be encompassed by the cited language. The present claims do not include this terminology. Thus, this rejection no longer applies.

(B) Claims 21-23 were rejected as indefinite, the Office arguing that "it is not clear whether 'capable of binding to E2 of HCV' is a required property of the recited variants or fragments, or is only required for the 24 kD protein." Office Action, page 7. Claims 21-23 have been amended to make clear that both the 24 kD protein and the fragment thereof bind E2. Thus, this basis for rejection has been overcome and withdrawal thereof is respectfully requested.

(C) Claims 21-24 were asserted to be indefinite based on the terminology "capable of binding." The claims have been amended to eliminate this terminology. Thus, this rejection no longer applies.

(D) Claim 25 was rejected as indefinite due to the purported lack of antecedent basis for the terms "the functional portion" and "the transmembrane domain." Claim 25 has been amended to read "a" functional portion and "a"

transmembrane domain. Thus, this basis for rejection has been overcome. Withdrawal thereof is respectfully requested.

(E) Claim 27 was rejected under 35 U.S.C. §112, second paragraph, based on the use of the term "hyperexpresses" because it is a relative term. Applicant traverses the rejection. As explained in MPEP, §2173.05(b), the use of relative terms does not automatically render a claim indefinite. Instead, "[a]cceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification." The specification, at page 20, lines 15-19 explains that the cell line prepared by applicant that hyperexpressed the 24 kD protein "showed a markedly greater binding affinity for E2 than the wild-type strain." Thus, one of skill in the art, with reference to the specification, would understand the meaning of the term "hyperexpresses."

The Examiner acknowledges that the specification describes a selection process for MOLT4 cells that express more of the 24 kD protein than the original MOLT4 line. However, the Examiner states that how much additional expression is required is not clear. Under 35 U.S.C. §112, second paragraph, absolute specificity and precision are not required in the claims. Claims need only reasonably apprize a person having ordinary skill in the art as to their scope. *Hybritech Inc., v. Monoclonal Antibodies, Inc.,* 231 USPQ 81, Fed. Cir. 1986. A claim which is clear to one ordinarily skilled in the art when read in light of the specification, does not fail for indefiniteness. *Allan Archery, Inc. v. Browning Manufacturing Co.*, 819 F.2d 1087, 2 USPQ2d 1490 (Fed. Cir. 1987). The specification teaches that hyperexpression requires that the expression of the 24 kD protein be greater than the original. Thus, the specification provides a reasonable degree of precision, and one of skill in the art would understand the metes and bounds of the invention. The Examiner is respectfully requested to withdraw the rejections under 35 U.S.C. §112, second paragraph.

Rejections Over the Art:

Claims 22 and 24-40 were rejected under 35 U.S.C. §102(b) as anticipated by, or in the alternative, under 35 U.S.C. §103(a) as unpatentable over Levy et al. (1991) *J. Biol. Chem.* 266:14597-14602 in view of Levy et al. (1998) *Annu. Rev. Immunol.* 16:89-109 and Pileri et al. (1998) *Science* 282:938-941. The Examiner states that Levy et al. describes TAPA-1 which "reasonably appears to be identical to the protein claimed except that Levy et al. 1991 is silent as to the inherent functional characteristic of specifically binding to HCV E2." Office Action, page 8. The Office further argues: "The composition of claim 22 is not distinguished from compositions disclosed by Levy et al. since the combination of a protein and a pharmaceutical carrier represents an intended use." Office Action, page 9. Applicant traverses the rejection.

As an initial matter, applicant assumes the rejection is made solely over Levy et al., 1991, as the remaining references published after applicant's priority date of 1997. However, Levy et al., 1991, fails to either anticipate or render obvious the claimed invention. To anticipate a claim, a single source must contain all of the elements of the claim. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 USPQ 81, 90 (Fed. Cir. 1986). *Atlas Powder Co. v. E. I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1574, 224 USPQ 409, 411 (Fed. Cir. 1984). Moreover, the single source must disclose all of the claimed elements "arranged as in the claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 9 USPQ 2d 1913, 1920 (Fed. Cir. 1989); *Connell v. Sears Roebuck & Co.*, 722 F.2d 1542, 1548, 220 USPQ 193, 198 (Fed. Cir. 1983). Finally, the law requires identity between the claimed invention and the prior art disclosure. *Kalman v. Kimberly-Clar Corp.* 713 F.2d 760, 771, 218 USPQ 2d 781, 789 (Fed. Cir. 1983, cert. denied, 465 U.S. 1026 (1984)).

Levy et al., 1991, does not describe a composition or method of use as claimed and therefore cannot anticipate the present claims. In fact, the last paragraph of Levy states: "The functions of the TAPA-1 related family of proteins

are currently unknown." Certainly, then, Levy also provides no motivation to formulate the protein into a pharmaceutical composition since the function of the protein is unknown. The fact that Levy's protein may have the "inherent property" of binding HCV E2 is of no import. It is axiomatic that a retrospective view of inherency, such as proposed by the Office, is not a substitute for some teaching or suggestion to arrive at the claimed invention. That which may be inherent is not necessarily known, and obviousness cannot be predicated on the unknown. See, e.g., *In re Newell*, 13 USPQ2d 1248 (Fed. Cir. 1989). Therefore, withdrawal of the rejections over the art is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims define a patentable invention. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please direct all further written communications in this application to:

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Appendix A

Version with Markings to Show Changes Made

In the Claims:

Claims 21-23 and 25-29 have been amended as follows:

21. (Amended) A method for treating a patient infected with hepatitis C virus (HCV) comprising administering to said patient an amount of [a] an unglycosylated, transmembrane protein having a molecular weight of about 24 kd as determined by SDS-PAGE, or a [functionally equivalent variant or] fragment thereof, [and capable of binding] wherein said protein is stable to acetone precipitation, and further wherein said protein or said fragment thereof specifically binds to the E2 protein of HCV, effective to reduce the infectivity of the virus.

22. (Amended) A composition comprising [a] an unglycosylated, transmembrane protein having a molecular weight of about 24 kd as determined by SDS-PAGE, or a [functionally equivalent variant or] fragment thereof, [and capable of binding to E2 of HCV,] in combination with a pharmaceutically acceptable carrier, wherein said protein is stable to acetone precipitation, and further wherein said protein or said fragment thereof specifically binds the E2 protein of hepatitis C virus.

23. (Amended) A process for preparing a [pharmaceutical] composition, said process comprising combining [in which] [a] an unglycosylated, transmembrane protein having a molecular weight of about 24 kd as determined

by SDS-PAGE, or a [functionally equivalent variant or] fragment thereof, [and capable of] with a pharmaceutically acceptable carrier, wherein said protein is stable to acetone precipitation, and further wherein said protein or said fragment thereof specifically [binding] binds to the E2 protein of hepatitis C virus[, is combined with a pharmaceutically acceptable carrier].

25. (Amended) The [protein] composition of claim [24] 22, wherein the protein lacks a functional portion of a transmembrane domain.

26. (Amended) The [protein] composition of claim [24] 22, wherein the protein is produced by a method comprising:

(a) providing a mammalian cell that expresses said 24 kd protein;

(b) recovering and solubilizing membranes from said mammalian cell to provide a cell membrane preparation;

(c) subjecting the cell membrane preparation to ammonium sulfate precipitation at less than 33% saturation and retaining the supernatant;

(d) subjecting the supernatant to ammonium sulfate precipitation at between 33% and 50% saturation and retaining the precipitate;

(e) resuspending the precipitate; and

(f) subjecting the precipitate to hydrophobic interaction chromatograpy and recovering the nonretained material.

27. (Amended) The [protein] composition of claim 26, wherein the mammalian cell that expresses said 24 kd protein hyperexpresses said 24 kd protein.

28. (Amended) The [protein] composition of claim 27, wherein the mammalian cell is a MOLT-4 cell.

29. (Amended) The [protein] composition of claim 28, wherein the cell membrane preparation is a plasma cell membrane preparation.

Claims 24 and 30-40 have been canceled.

Appendix B

Currently Pending Claims

21. (Amended) A method for treating a patient infected with hepatitis C virus (HCV) comprising administering to said patient an amount of an unglycosylated, transmembrane protein having a molecular weight of about 24 kd as determined by SDS-PAGE, or a fragment thereof, wherein said protein is stable to acetone precipitation, and further wherein said protein or said fragment thereof specifically binds to the E2 protein of HCV, effective to reduce the infectivity of the virus.

22. (Amended) A composition comprising an unglycosylated, transmembrane protein having a molecular weight of about 24 kd as determined by SDS-PAGE, or a fragment thereof, in combination with a pharmaceutically acceptable carrier, wherein said protein is stable to acetone precipitation, and further wherein said protein or said fragment thereof specifically binds the E2 protein of hepatitis C virus.

23. (Amended) A process for preparing a composition, said process comprising combining an unglycosylated, transmembrane protein having a molecular weight of about 24 kd as determined by SDS-PAGE, or a fragment thereof, with a pharmaceutically acceptable carrier, wherein said protein is stable to acetone precipitation, and further wherein said protein or said fragment thereof specifically binds to the E2 protein of hepatitis C virus.

25. (Amended) The composition of claim 22, wherein the protein lacks a functional portion of a transmembrane domain.

26. (Amended) The composition of claim 22, wherein the protein is produced by a method comprising:

(a) providing a mammalian cell that expresses said 24 kd protein;

(b) recovering and solubilizing membranes from said mammalian cell to provide a cell membrane preparation;

(c) subjecting the cell membrane preparation to ammonium sulfate precipitation at less than 33% saturation and retaining the supernatant;

(d) subjecting the supernatant to ammonium sulfate precipitation at between 33% and 50% saturation and retaining the precipitate;

(e) resuspending the precipitate; and

(f) subjecting the precipitate to hydrophobic interaction chromatograpy and recovering the nonretained material.

27. (Amended) The composition of claim 26, wherein the mammalian cell that expresses said 24 kd protein hyperexpresses said 24 kd protein.

28. (Amended) The composition of claim 27, wherein the mammalian cell is a MOLT-4 cell.

29. (Amended) The composition of claim 28, wherein the cell membrane preparation is a plasma cell membrane preparation.

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1: J Gastroenterol Hepatol 2001 Nov;16(11):1274-81 Related Articles, Links

Online

High viral loads, serum alanine aminotransferase and gender are predictive factors for the development of hepatocellular carcinoma from viral compensated liver cirrhosis.

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BACKGROUND AND AIMS: The aims of the present study were to determine the occurrence rate of hepatocellular carcinoma (HCC) and to assess the risk factors for the development of HCC in compensated viral liver cirrhosis. METHODS: Two hundred and thirty-nine cirrhotic patients (65 hepatitis B surface antigen (HBsAg) positive, 165 hepatitis C virus (HCV) antibody positive (anti-HCV), and nine with both HBsAg and anti-HCV positivity) were studied. The Kaplan-Meier method evaluated by a log-rank test was used to estimate the cumulative probability of HCC development. Independent predictors of HCC development were estimated by using the Cox proportional hazard regression analysis. RESULTS: Dual infection manifested as HBsAg and anti-HCV positive was the highest risk of HCC. Multivariate analysis indicated that anti-HCV positive, HBsAg positive, and lactate dehydrogenase were independent predictors of the development of HCC among individuals with viral cirrhosis. In the HBsAg-positive group, a high-titer of HBV-DNA (more than 3.7 log genome equivalents (LGE)/mL) was most predictive of HCC development. In the anti-HCV-positive group, male gender and a high-titer of HCV-RNA (more than 1.0 Meq/mL) were predictive factors for the development of HCC. CONCLUSIONS: Individuals with high viral loads should be monitored for the development of HCC. Clinical efforts at eradicating or reducing the viral load may reduce the risk for HCC.

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